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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,324	03/29/2004	Heidi A. Tissenbaum	UMY-035	5837

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LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/813,324	TISSENBAUM ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *5,6,8,27,29 and 49-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9-26,28 and 30-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-56* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 22 August 2006 have been entered. Claims 1 – 56 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group I, cholinergic pathway, muscarinic receptor, and DAF-2 in the reply filed on 22 August 2006 is acknowledged. In the restriction requirement mailed 17 July 2006, the examiner requested that applicant provide a listing of which claims are readable on the elected species. See restriction requirement, p. 5, underlined text. Applicant did not provide such a list, so the examiner has determined that the following claims read on the elected species: Claims 1 – 4, 7, 9 – 26, 28, 30 – 48. Should applicant disagree with the examiner's conclusion as to which claims read on the elected invention and species, applicant should explicitly indicate which of claims 5 – 6, 8, 27, 29, and 49 – 56 in fact encompass the elected invention.

3. Claims 5 – 6, 8, 27, 29, and 49 – 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 22 August 2006.

4. Claims 1 – 4, 7, 9 – 26, 28, and 30 – 48 are under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention..

Claims 1 – 4, 7, 9 – 26, 28, and 30 – 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for contacting organisms or cells with candidate compounds, does not reasonably provide enablement for all deregulated neurotransmitter pathways as broadly claimed, or for all detectable phenotypes, or for identification of agents capable of enhancing longevity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors

include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case the nature of the invention, identifying agents which increase longevity, is complex. With the exception of claims 21 – 23 and 40, which are limited to nematodes, the claims read on all species. Longevity enhancement is quite complex, and the art teaches that while certain interventions such as caloric restriction appear to extend longevity in a species-independent manner (see Lane et al., 2002. Microscopy Research and Technique 59:335-338, who teach that caloric restriction extends life-span in nearly all species tested), the signaling pathways that underlie this extension are complex and difficult to generalize. The specification presents data obtained from the nematode *C. elegans*, but presents no data from humans or any other mammals. While the role of insulin signaling pathways in the aging of *C. elegans* was well-understood at the time of the invention (see for example Nelson 2003. Genes & Development 17:813-818 for a review) the art cautions that the findings obtained in this species are not easily extendable to mammals or other tetrapods. See for example Tatar (2003) Science 299:1346-1351, who teaches that over the course of evolution there have been significant duplications of genes and changes in physiology which make it difficult to extend the findings on extension of longevity of any one species to all species in general. While the action of insulin and IGF proteins may be local in flies and worms, it is systemic in mammals and other tetrapods (p. 1350). Tatar teaches that considerable further research is needed to find aging-related targets of insulin and the insulin pathway in tetrapods (i.e., including mammals, encompassed by all claims except 21 – 23 and 40, and explicitly recited in claims 38 – 39). As the specification contains no working examples of the screening methods claimed successfully identifying longevity-enhancing compounds in mammals, and the art teaches that the findings obtained in *C. elegans* cannot be extended to mammals without considerable additional research, it would take undue experimentation to practice the invention for the scope of any animal beyond nematodes.

Furthermore, the claims as written would not reasonably be expected to identify agents which are enhancers of longevity. For example, claim 1 requires contacting an organism with a test agent, wherein the organism has a deregulated neurotransmitter signaling pathway,

measuring a phenotype "associated with" the pathway, and concluding that an agent which modulates the phenotype is a longevity-enhancing agent. The method steps set forth would not be expected to find those agents which extend longevity. For example, Bymaster (2003. European Journal of Neuroscience 17:1403-1410) teaches contacting mice with dysregulated cholinergic signaling pathways (deletions of any one of the muscarinic M1 – M5 receptors) with pilocarpine. Mice lacking M1 survive the injection, but wild-type mice and those lacking any one of M2 – M5 all die within an hour of administration of the drug (see p. 1407, second column). The reference teaches every step of the method of claims 1, 3 – 4, 14 – 17, 24 – 26, 28, 30 – 31, 38, 41 – 47, however rather than identifying pilocarpine as a longevity-enhancing agent, as directed by the claims, the reference correctly teaches that this substance is toxic. Clearly it is not a longevity enhancing agent, as it kills most of the mice who receive it within an hour. Note that many of the claims do not require any specific mutations, or any mutations at all (see for example claims 14 – 15 which only require that certain pathways be present, not mutated). As the claimed methods will identify toxic molecules, the artisan would have to determine how to modify the methods such that longevity-enhancing molecules will instead be identified. This places an unreasonable burden on the artisan to further modify the method so that it is operative.

Additionally, many of the dependent claims recite mutually exclusive limitations, such that if one were in fact enabled the other would necessarily not be enabled. See for example claim 30, wherein the agent is identified based on its ability to activate neurotransmitter signaling, and claim 31, wherein the agent is identified based on its ability to inhibit neurotransmitter signaling. If an agent that activates neurotransmitter signaling is one that extends longevity, then one that inhibits the same function would be expected to have the opposite effect, i.e. it would be expected to shorten longevity. The specification does not provide adequate guidance to the artisan to allow him to determine when enhancement (as opposed to inhibition) of signaling is indicative that the agent is longevity-enhancing. Note that the prior art teaches that in *C. elegans*, those substances which decrease DAF-2 activity would be expected to be longevity-enhancing (Ruvkun US Patent Application Publication 2001/0029617, paragraph [0443]). Thus in order to practice the methods commensurate in scope with the claims, the artisan would have to invent this aspect of the method himself.

The specification does not provide adequate enablement for the full scope of neurotransmitter pathways as generically claimed, and does not provide enablement for all

phenotypes associated with neurotransmitter pathways as claimed. A phenotype could be anything, as long as it is measurable. Many phenotypes associated with neurotransmitter pathways have nothing whatsoever to do with longevity. Similarly, many pathways have nothing to do with longevity. For example, Parkinson's disease is a phenotype associated with dysregulation of the dopaminergic pathway, depression is a phenotype associated with dysregulation of the serotonergic pathway. Few of the claims under examination are limited to those neurotransmitter pathways which are known to be involved in extending longevity in nematodes. Finding modulators of phenotypes other than longevity would not be expected to identify agents which are longevity enhancers.

Given the breadth of the claims, the complex nature of the invention, the state of the art, and the few working examples in the specification, it would take an undue amount of experimentation in order for the artisan of ordinary skill to practice the invention commensurate in scope with the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 – 31, 38 – 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30, 31, 38 – 40 each recites the limitation "said cell" or "the cells". There is insufficient antecedent basis for this limitation in the claim. The claims depend from each of claims 24 – 26. Claim 26 is drawn to a cell population. This parent claim does not provide proper antecedent basis for "said cell".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14 – 18, 21 – 22, 24 – 26, 28, 30, 40 – 43, and 45 – 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruvkun (US Patent Application 2001/0029617, published 11 October 2001).

Ruvkun teaches contacting organisms with test agents, assaying for the ability of the agent to affect an indicator of the pathway, and identifying said agents as longevity-enhancers. See specifically paragraphs [0443] – [0445], drawn to screens for isolating longevity therapeutics. Note that claim 14 does not require any particular phenotype to be measured, and does not require any particular neurotransmitter signaling pathway to be present. As the assays of Ruvkun are to be performed on worms, which have multiple signaling pathways including instantly-elected cholinergic pathways, and the reference teaches measuring phenotypes such as DAF-2 activity, it reasonably meets every limitation of claim 14. Furthermore, as claim 15 requires the presence of an insulin signaling pathway, which is necessarily present in *C. elegans* worms, the reference also anticipates the method of claim 15.

Claim 16 is rejected as the reference by Ruvkun teaches that in the assays described in the invention reporter genes can be used (see for example paragraphs [0416] – [0422]). Claims 17 and 19 are rejected as Ruvkun teaches measurement of expression and activity of reporters such as GFP and luciferase (see paragraphs [0419] – [0422]). The reference also teaches that GFP in particular can be used to determine subcellular localization of the labeled protein (see paragraph [0421]) which is on point to claim 18. Claims 21 – 22 are rejected as they depend from rejected claims 14 and 15 and the reference teaches performing the assays on *C. elegans* nematodes.

Claims 24 – 26 are rejected as the reference teaches contacting nematodes with muscarinic agonists and measuring dauer recovery (see paragraph [0410]). As nematodes have both neurotransmitter and insulin pathways, and the worms include populations of cells, and dauer recovery is an indicator of cholinergic signaling, the reference teaches all limitations of claims 24 – 26. Claim 28 is rejected as the muscarinic agonists work at cholinergic pathways and in fact muscarinic receptors are a subset of cholinergic receptors. Claim 30 is rejected as the agonists activate muscarinic signaling in the cells. Claim 40 is rejected as the cells are not only derived from a nematode, they are in fact contained in a nematode. Claim 41 is rejected as the nematodes contain both pre- and post-synaptic cells. Claims 42 – 43 are rejected as acetylcholine is used as a transmitter between neurons in *C. elegans*.

Claim 45 is rejected because the reference by Ruvkun teaches contacting nematodes with test compounds and detecting the activity or expression of the appropriate neurotransmitter signaling pathway. See for example paragraph [0410]; note that nothing in claim 45 excludes in vivo *C. elegans* from "an assay composition". The reference by Ruvkun teaches assays involving *C. elegans*, so they are clearly an assay composition as recited in claim 45. Claim 46 is rejected as Ruvkun teaches dauer recovery is induced by muscarinic agonists, thus this is reasonably an activity of the muscarinic receptors in the worms.

8. Claims 1, 3 – 4, 14 – 16, 24 – 26, 28, 30, 33, 38, 41 – 43, 45, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Gomeza (2001. Life Sciences 68:2457 – 2466).

Gomeza teaches administering oxotremorine to mice with wild-type and mutated muscarinic receptors. See for example Figure 1. The M2 and M4 knockout mice reasonably are animals with deregulated neurotransmitter systems, as they lack these muscarinic receptors which are receptors for the neurotransmitter acetylcholine. The reference teaches measuring a phenotype associated with the receptor, namely tail-flick and hot plate test responses and comparing to suitable controls (see Figure 1, wherein "vehicle" is a suitable control). Thus the reference teaches every element of claim 1. Note that claim 1 is not limited to measuring longevity as a phenotype, and the final step permits one to identify the agent based solely on its ability to alter the phenotype. Claims 3 and 4 are rejected as the references teaches deregulated muscarinic receptors.

Claim 14 is rejected as the reference teaches all steps of the method: contacting organisms with test agents, assaying for ability of the agent to affect an indicator of the signaling pathway (namely the responses in Figure 1), and identifying the agent based on its ability to alter the indicator. Claim 15 only requires the additional limitation that the organism have an insulin signaling pathway; as mice necessarily have such a pathway the reference anticipates this claim as well. Claim 16 is rejected as the pain responses are indicators of the function of the muscarinic receptors. Claims 24 – 26 are rejected as the reference teaches contacting cells (contained in mice), a cell (contained within mice), and a cell population (contained in mice) with a test agent; in each case the cells have both insulin- and neurotransmitter-signaling pathways. The reference also teaches detecting an indicator (namely the behavioral outputs in Figure 1), and identifying agents based on their ability to modulate muscarinic neurotransmission in the cells. Claim 28 is rejected as the cells contain muscarinic cholinergic pathways. Claim 30 is

rejected as oxotremorine is an agonist of muscarinic receptors (see Gomeza, p. 2459, second complete paragraph). Claim 33 is rejected as the behavioral assays in Gomeza are reasonably "a reporter" of the muscarinic receptor pathway molecules. While certain terms are explicitly defined on pp. 10 – 13 of the specification, "reporter" is not one of them and thus could reasonably encompass anything that reports the relevant activity. Claim 38 is rejected as the mouse cells are mammalian. Claims 41 – 43 are rejected as the cells comprise pre- and post-synaptic neurons. Claim 45 is rejected as the reference by Gomeza teaches contacting a mouse (i.e. an assay composition) with a test agent, detecting activity of the muscarinic pathway as indicated by the behavioral responses, and identifying the agent based on its ability to modulate the activity. Claim 47 is rejected as the reference teaches that oxotremorine is agonist of muscarinic receptors.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14 – 18, 21 – 26, 28, 30, 40 – 43, and 45 – 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun (US Patent Application 2001/0029617).

The reasons why claims 14 – 18, 21 – 22, 24 – 26, 28, 30, 40 – 43, and 45 – 46 are anticipated by Ruvkun are set forth in the rejection above under 35 USC 102(b). Ruvkun further teaches using the parasitic nematode *A. caninum* in some screening assays such as for finding nematicides and teaches the similarity of the biochemical pathways in *C. elegans* and *A. caninum*, and thus is on point to claim 23. However Ruvkun does not teach performing the

screening assay for identifying agents which *enhance longevity* as recited in claims 1, 14, and 15, in a parasitic nematode.

It would have been obvious to one of ordinary skill in the art to perform the screening assays for longevity-enhancing compounds from Ruvkun on parasitic nematodes, with a reasonable expectation of success. The motivation to do so would be to find longevity-enhancing compounds. It would be reasonable to expect success, as Ruvkun teaches that the biochemical pathways found in *C. elegans* are also present in the parasitic nematode *A. caninum*. It is obvious to substitute one screening organism for another as both were known to be similarly suitable for the same purpose in the prior art; see MPEP § 2144.06.

Conclusion

10. No claim is allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Fordyce et al. 1991. J. Gerontol. 46:B245-248. The reference teaches that those animals subject to caloric restriction, which is known to increase longevity, have increased muscarinic receptor density in the brain when old. However the reference does not teach or suggest screening for longevity-enhancing compounds but rather points to the effects of longevity-extending phenomena on the cholinergic pathways.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
November 1, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER